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(54) Title: METHOD AND COMPOSITION FOR PROMOTING HAIR GROWTH			
(57) Abstract			
Trichogenous compositions and methods of stimulating hair growth with concomitant alopecia retardation comprise nicotinic acid, d- α tocopherol, dimethyl sulfoxide, and, optionally, β -carotene, ethanol, or both.			

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METHOD AND COMPOSITION FOR PROMOTING HAIR GROWTH**Field of the Invention**

The invention relates to compositions and methods for treating hair loss and for promoting hair growth.

5 Background of the Invention

Human hair growth and re-growth (trichogenesis) are dependent on the activity of the hair follicles. This activity is cyclic and essentially entails three phases, *i.e.*, the anagen phase, the catagen phase, and the telogen phase. The active anagen (or growth) phase lasts for several years during which the hair elongates. The anagen 10 phase is succeeded by a very short and transient catagen phase, followed by a rest (or quiescent) phase referred to as the telogen phase, which lasts a few months. At the end of the rest period, the hair is shed and another cycle begins anew. Hair thus is being constantly renewed and, of the approximately 150,000 hair follicles on a human head, approximately 10% are at rest at any given time and thus will be replaced in a 15 few months, *i.e.*, at the end of the telogen phase.

Various conditions may interrupt, impede, or alter the normal hair growth cycle. Once such condition is alopecia, which is identified generally by a disturbance of hair renewal. Alopecia initially accelerates the frequency of the aforementioned cycle at the expense of the quality of the hairs. Thereafter, a gradual depletion of the number 20 of active hair follicles in an area through regression of so-called "terminal" hair reduces the quantity of hair. Some regions of the body are affected more than others. In particular, the temporal or frontal areas in men and a diffuse portion of the crown in women typically are more severely affected than other regions of the body.

Androgenic alopecia, the most common form of hair loss in both sexes, is an 25 autosomal dominant genetic condition which results in a progressive reduction of hair follicle mass. A progressive reduction in hair follicle size results in multiple common patterns of scalp hair loss, often resulting in eventual total baldness. The progression of androgenic alopecia is marked by the transition of terminal hair to the fine, thin,

non-pigmented villus type of hair. Ultimately, complete loss of hair growth leads to balding. The prevalence of this genetic predisposition has led to an enormous body of research in an effort to find an effective treatment.

However, treatments for alopecia, including androgenic alopecia, developed to date have achieved only limited success. Such treatments include massage techniques, electric current stimulation, heat application, and the topical application of various agents. Among various treatments for alopecia, topical delivery of a treatment or medicament is preferred because it reduces or avoids systemic side effects while providing improved local delivery of the treatment or medicament. A disadvantage of topical delivery, however, is the difficulty associated with penetration of the epidermis. The epidermal barrier, composed of keratinized cells without nuclei, is a barrier to most topically applied agents. Agents with increased ability to penetrate the epidermal layer include low molecular weight molecules and lipophilic substances. Transdermal delivery of a medicament is improved by a number of agents including, for example, dimethyl sulfoxide (DMSO) as described in U.S. Patent 3,551,554.

One agent that exhibited some success in treating alopecia is the antihypertensive agent minoxidil, which is described in U.S. Patents 4,139,619 and 4,596,812. Though minoxidil stimulates the growth of new villus hair and some growth of terminal hair, it has a significant failure rate in many subjects. Thus, the re-growth of terminal scalp hair is not satisfactorily achieved by minoxidil treatment.

Other approaches for treating alopecia include the use of pyrimidine derivatives as active hair growth ingredients. See, e.g., U.S. Patents 5,846,552; 5,772,990; 5,466,694; and 5,328,914. U.S. Patent 5,328,914 to Hocquaux *et al.*, for example, relates to compositions for treating hair loss including pyrimidine 3-oxide derivatives which also may include, among many other things, an organic solvent, hyperemics, UV-A and UV-B screening agents, antioxidants, free radical scavengers, moisturizing agents, anti-inflammatory agents, anti-bacterial agents, and vitamins. Other active ingredients for treating hair loss include (benzo-1,2,4-thiadiazine)-1,1-dioxide derivatives as described in U.S. Patent 4,985,425. These compositions, however, also have exhibited only limited success in treating hair loss and in stimulating hair growth.

Thus, there remains an unfulfilled need for a composition and method which are effective in stimulating and inducing desirable terminal hair growth.

Summary of the Invention

The present invention is directed to trichogenous compositions and methods for inducing and stimulating hair growth with concomitant alopecia retardation. The trichogenous composition of the invention comprises nicotinic acid, d- α tocopherol, and dimethyl sulfoxide. A method for treating alopecia or inducing and stimulating hair growth comprises administering a therapeutically effective amount of a composition comprising nicotinic acid, d- α tocopherol, and dimethyl sulfoxide. Preferably, the composition further comprises β -carotene, ethanol, or both.

Detailed Description of the Preferred Embodiments

The trichogenous composition according to one embodiment of the invention comprises nicotinic acid, d- α tocopherol, and dimethyl sulfoxide (DMSO). Unless otherwise indicated, the weight percentages noted below are based on the total weight of the trichogenous composition. The various components of the trichogenous composition according to the invention described below are most preferably provided in amounts sufficient to promote the desirable hair growing or hair loss arresting properties thereof, while substantially or totally avoiding undesirable physiological side effects known to be associated with the various components thereof when applied topically. Examples of undesirable side effects are well known as recited in *Remington's Pharmaceutical Sciences* (1980 *et seq.*). Typically, the concentration of nicotinic acid ranges from about 0.001 to about 6 wt%, preferably about 0.001 to about 3 wt%, more preferably from about 0.1 to about 2 wt%, and even more preferably from about 1.2 to about 1.6 wt%. The concentration of d- α tocopherol preferably ranges from about 0.1 to about 30 wt%, more preferably from about 1 to about 20 wt%, and even more preferably from about 9 to about 12 wt%. DMSO concentration preferably ranges from about 40 to about 99 wt%, more preferably from about 60 to about 90 wt%, and even more preferably from about 70 to about 80 wt%.

According to another embodiment of the invention, the composition further comprises β -carotene, ethanol, or both. β -carotene concentration may range from about 0.0009 to about 5 wt%, preferably from about 0.005 to about 2 wt%, and more preferably from about 0.1 to about 0.5 wt%. Ethanol concentration may range from about 0.1 to about 30 wt%, preferably from about 8 to about 20 wt%, and more preferably from about 10 to 12 wt%.

Other components which may be present include, for example, one or more of vitamin A; vitamin B; vitamin B₆; vitamin C; melatonin; glycolic acid; pycnogenol; ethylene glycol; propylene glycol; glutathione; amino acids such as arginine, ornithine, and tyrosine; hyaluronic acid or a sodium salt thereof; panthenol; trace minerals; fragrance; colorant; zeronol; estradiol; estrone; estriol; tamoxifen; finasteride; raloxifene; clomiphene; spironolactone; ketoconazole; cyproterone; cimetidine; saw palmetto extracts; minoxidil; and prostaglandin D2 or analogs thereof. Exemplary trace metals which may be present include selenium, zinc, and/or iron.

According to one embodiment, the composition of the present invention preferably is free or substantially free of pyrimidine 3-oxide and pyrimidine N-oxide derivatives as taught, for example, by U.S. Patents 5,846,552, 5,772,990, 5,466,694, and 5,328,914, each of which is incorporated herein by reference in its entirety. In addition, according to still another embodiment of the present invention, the composition preferably is free or substantially free of (benzo-1,2,4-thiadiazine)-1,1-dioxide derivatives as taught by U.S. Patent No. 4,985,425, incorporated herein by reference in its entirety.

Within the compositions according to the invention, a pharmaceutically acceptable carrier may be provided to facilitate topical application thereof. Various carriers containing a physiologically compatible medium appropriate for topical application are well known to those skilled in the art. See, e.g., *The United States Pharmacopeia* (1984); *Remington's Pharmaceutical Sciences* (1980), each incorporated herein by reference in its entirety. Exemplary formulations of the invention may include carrier(s) such as perfume(s), fragrance(s), skin moisturizer(s), skin lotion(s), skin conditioner(s), exfoliant(s), cosmetic(s), cosmetics removal

agent(s), hair setting lotion(s), hair oil treatment(s), aftershave(s), shaving lotion(s), hair mousse(s), hair conditioner(s), hair repairing agent(s), astringent(s), skin cleanser(s), hair cleanser(s), shampoo(s), hair dye(s), hair bleaching agent(s), and preferred combinations thereof.

5 The compositions according to the invention may be used for treating hair loss or for stimulating hair growth by applying therapeutically effective amounts of the composition to areas of the skin where hair growth is desired. Exemplary therapeutically effective amounts are from about 100 μ l to about 2 ml per 50 square centimeters of skin, preferably from about 0.5 ml to about 1 ml per 50 square centimeters of skin. The treatment may be applied in single or divided daily doses, for example, one to three or more times per day. The composition may be massaged onto the skin area, for example, for 15 to 60 seconds per application. The area of skin to be treated preferably is washed, e.g., with soap and water, immediately prior to applying the treatment in order to maximize absorption of the components.

10 15 As will be appreciated by those skilled in the art, the compositions according to the invention also are effective for treating various skin conditions such as, for example, burns, photo damaged skin, dermatoheliosis, skin wrinkles, seborrheic dermatitis, dandruff, eczema, acne, psoriasis, cutaneous, systemic circulation, itching, and rashes.

20 25 Without desiring to be bound by any particular theory, dimethyl sulfoxide (DMSO) is believed to function as a transdermal carrier of nicotinic acid, d- α tocopherol, β -carotene, and ethanol. DMSO enhances the percutaneous penetration and absorption of these ingredients. DMSO and ethanol not only serve as solvent for nicotinic acid, d- α tocopherol, and β -carotene, but also enhance subcutaneous absorption and/or penetration of d- α tocopherol and β -carotene. β -carotene and d- α tocopherol also provide a mechanism for extended (e.g., slow) release of the components or the composition of the invention. Ethanol enhances transdermal penetration of nicotinic acid, d- α tocopherol, and β -carotene.

30 Perifollicular circulation also is believed to be enhanced by increased vascular dilation which is caused by topical application of nicotinic acid. The absorption of

nicotinic acid produces dramatic dilation of local capillaries and arterioles, which dilation is believed to be a phenomenon mediated by a local increase in prostaglandin D2 concentration. The vascular dilation elicited by nicotinic acid also significantly increases local blood delivery to the hair follicles in treated areas. A subject typically 5 experiences a notable flushing sensation resulting from this prostaglandin-mediated vascular dilation. Local circulation also is enhanced by the vasodilative response attributable to DMSO and ethanol. The benefits of improved local circulation are further enhanced by the concomitant absorption of antioxidants, with a simultaneous and dramatic increase in local concentration of the antioxidants of the treatment 10 composition.

Again, without desiring to be bound by any particular theory, it is believed that d- α tocopherol and β -carotene also reduce free radical damage in areas where hair growth stimulation or alopecia retardation is desired. β -carotene is very effective 15 antioxidant, especially at the low oxygen tensions prevalent in the body. The ability of β -carotene to neutralize free radicals provides protection to hair follicles from free radical damage. D- α tocopherol, due to its lipophilic structure, tends to accumulate in cell membranes and fat deposits, where it rapidly neutralizes molecular oxygen and free radicals. Local cell membranes, including those of the treated hair follicles, are 20 protected from damaging peroxidation reactions that occur in the presence of the aforementioned free radicals. Both β -carotene and d- α tocopherol are lipophilic and tend to accumulate in fat deposits, thereby providing extended local follicular protection and resultant hair growth enhancement.

EXAMPLES

The following examples are illustrative of preferred aspects of the invention and 25 are not intended to limit its scope.

Example 1

A trichogenous composition was prepared by combining 50 ml DMSO, 10 ml ethanol, d- α tocopherol (10000 IU activity), β -carotene (250000 IU activity), 1000 mg

of nicotinic acid, and water. The composition thus-prepared had 77% wt% DMSO, 11.05 wt% ethanol, 10.29 wt% d- α tocopherol, 0.22 wt% β -carotene, 1.40 wt% nicotinic acid, and the balance water.

Example 2

5 A 28-year old male bodybuilder with a history of anabolic steroid use was diagnosed with accelerated male pattern alopecia, likely resulting from androgen abuse. The subject otherwise was without health problems and was not using any medications immediately prior to the trial. The subject had only villus hair growth in the crown area and complete bilateral frontal hair loss in the fronto-parietal regions.
10 The frontal areas of hair loss were approximately 2 cm x 5 cm and 3 cm x 5 cm, respectively.

15 The subject began topical application of the composition of Example 1 once daily after hair washing. New terminal hair growth was noted after six weeks of treatment. Complete return of terminal growth was noted in the crown area after 12 weeks of treatment. Approximately 85% of terminal growth was restored in the frontal region after 18 weeks with the remaining 15% skin surface in the frontal areas exhibiting villus growth. Complete hair regrowth was noted at 24 weeks.

Example 3

20 A 30-year old black male with a family history of androgenic alopecia with a two-year history of frontal hair loss exhibited only villus hair growth in the right fronto-parietal region in an area of 2 cm x 4 cm. The subject exhibited complete hair loss in the left fronto-parietal region in an area of 1 cm x 3 cm. The subject previously had failed one year of topical minoxidil therapy. The subject noted return of terminal hair growth on the right frontal region after 8 weeks of daily topical application of the composition of Example 1. The subject noted complete return of terminal hair growth on the left frontal region after 17 weeks of treatment.
25

Example 4

A 29-year old male bodybuilder abusing androgenic steroids with complaint of complete hair loss in the crown was treated. The subject reported that the hair loss began approximately 6 months after initiation of anabolic steroid use and progressed 5 rapidly to complete baldness in the crown area after one year. The subject admitted having no desire to stop androgen use and was using androgenic steroids at the time of treatment. The subject topically applied the composition of Example 1 to the crown area twice daily after hair washings. The subject noted villus growth after five weeks. The subject reported complete return of terminal hair growth in 24 weeks. The subject 10 thereafter decreased topical application to once daily and has since maintained hair growth without additional thinning.

It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions and methods of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that 15 the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents. All patents and publications cited herein are incorporated by reference in their entireties.

WHAT IS CLAIMED IS:

1. A trichogenous composition comprising nicotinic acid, d- α tocopherol, dimethyl sulfoxide, and optionally at least one of β -carotene and ethanol.
2. The composition of claim 1 comprising:
 - from about 0.001 to about 6 wt% nicotinic acid;
 - from about 0.1 to about 30 wt% d- α tocopherol;
 - from about 40 to about 99 wt% dimethyl sulfoxide;
 - from about 0.0009 to about 5 wt% β -carotene; and
 - from about 0.1 to about 30 wt% ethanol, based on a total weight of the composition.
3. The composition of claim 1 comprising:
 - from about 0.1 to about 2 wt% nicotinic acid;
 - from about 1 to about 20 wt% d- α tocopherol;
 - from about 60 to about 90 wt% dimethyl sulfoxide;
 - from about 0.005 to about 2 wt% β -carotene; and
 - from about 8 to about 20 wt% ethanol, based on a total weight of the composition.
4. The composition of claim 1 comprising:
 - from about 1.2 to about 1.6 wt% nicotinic acid;
 - from about 9 to about 12 wt% d- α tocopherol;
 - from about 70 to about 80 wt% dimethyl sulfoxide;
 - from about 0.1 to about 0.5 wt% β -carotene; and
 - from about 10 to about 12 wt% ethanol, based on a total weight of the composition.

5. The composition of claim 1 further comprising at least one compound selected from the group consisting of vitamin A, vitamin B, vitamin B₆, vitamin C, melatonin, glycolic acid, pycnogenol, ethylene glycol, propylene glycol, glutathione, amino acids, hyaluronic acid, a sodium salt of hyaluronic acid, panthenol, trace minerals, fragrance, and colorant.
6. The composition of claim 1 further comprising at least one compound selected from the group consisting of zeranol, estradiol, estrone, estriol, tamoxifen, finasteride, raloxifene, clomiphene, spironolactone, ketoconazole, cyproterone, cimetidine, saw palmetto extracts, minoxidil, and prostaglandin D2.
7. The composition of claim 1 further comprising at least one compound selected from the group consisting of arginine, ornithine, and tyrosine.
8. The composition of claim 1 further comprising at least one element selected from the group consisting of selenium, zinc, and iron.
9. The composition of claim 1 further comprising a pharmaceutically acceptable carrier.
10. The composition of claim 4 further comprising a pharmaceutically acceptable carrier.
11. The composition of claim 1 further comprising a carrier selected from the group consisting of perfume, fragrance, skin moisturizer, skin lotion, skin conditioner, exfoliant, cosmetics, cosmetics removal agent, hair setting lotion, hair oil treatment, aftershave, shaving lotion, hair mousse, hair conditioner, hair repairing agent, astringent, skin cleanser, hair cleanser, shampoo, hair dye, hair bleaching agent, and mixtures thereof.

12. The composition of claim 1, wherein the composition is substantially free of derivatives of pyrimidine 3-oxide, pyrimidine N-oxide, and (benzo-1,2,4-thiadiazine)-1,1-dioxide.
13. The composition of claim 12 further comprising a pharmaceutically acceptable carrier.
14. A method of stimulating hair growth comprising administering a therapeutically effective amount of the composition of claim 1.
15. A method of stimulating hair growth comprising administering a therapeutically effective amount of the composition of claim 2.
16. A method of stimulating hair growth comprising administering a therapeutically effective amount of the composition of claim 3.
17. A method of stimulating hair growth comprising administering a therapeutically effective amount of the composition of claim 4.
18. A method of stimulating hair growth comprising administering a therapeutically effective amount of the composition of claim 12.
19. A method for treating a skin condition selected from the group consisting of burns, photo damaged skin, dermatoheliosis, skin wrinkles, seborrheic dermatitis, dandruff, eczema, acne, psoriasis, cutaneous, systemic circulation, itching, and rashes, the method comprising administering a therapeutically effective amount of a composition comprising nicotinic acid, d- α tocopherol, dimethyl sulfoxide, and optionally at least one of β -carotene and ethanol.

20. A trichogenous composition consisting essentially of nicotinic acid, d- α tocopherol, dimethyl sulfoxide, and optionally at least one of β -carotene and ethanol.